Understanding the role of the R-spondin 2-LGR4 system in tongue squamous cell carcinoma progression

Al-Samadi, Ahmed

2019-06

Al-Samadi , A & Salo , T 2019 , ' Understanding the role of the R-spondin 2-LGR4 system in tongue squamous cell carcinoma progression ' , EBioMedicine , vol. 44 , pp. 8-9 . https://doi.org/10.1016/j.ebiom.201

http://hdl.handle.net/10138/313001
https://doi.org/10.1016/j.ebiom.2019.05.033

EBioMedicine 44 (2019) 8–9

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

Understanding the role of the R-spondin 2-LGR4 system in tongue squamous cell carcinoma progression

Ahmed Al-Samadi [a,b,*], Tuula Salo [a,b,c,d,e]

[a] Department of Oral and Maxillofacial Diseases, Clinicum, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[b] Translational Immunology Program, Faculty of Medicine, University of Helsinki, Finland
[c] Cancer and Translational Medicine Research Unit, University of Oulu, Oulu, Finland
[d] Medical Research Centre, Oulu University Hospital, Oulu, Finland
[e] Helsinki University Hospital, Helsinki, Finland

Squamous cell carcinoma (SCC) is a major type of solid cancer that is derived from squamous cells and may develop in several parts of the body. Head and neck (HN) SCC represent a high proportion of the total SCC cases, indeed HNSCC is the eighth most common malignancy [1] and is a major cause of death worldwide. Sadly, HNSCC patients have low five-year survival rate of around 50% [3]. It is unfortunate that this percentage has not essentially improved over the last few decades. This is still the challenging fact, in spite of considerable advances in our knowledge of SCC progression, and also the introduction of new therapies such as the use of targeted (cetuximab), and immuno (pembrolizumab and nivolumab) therapies. These facts highlight the need for further studies in this field, especially to understand more about the mechanisms underlying SCC cancer progression and to reveal novel molecules which could be targeted for therapeutic purposes.

In *EBioMedicine*, Zhang et al. studied the role of the R-spondin 2-LGR4 system in tongue (T) SCC as an example of SCC both in general, and HNSCC specifically [9]. Studying this system in TSCC is of profound importance mainly because 1) the R-spondin 2-LGR4 system had not been studied before in TSCC, and 2) there are conflicting results about its role in other solid cancers, such as colon, breast, and gastric cancer ([2,4,6,8,10]. The role of R-spondin 2 in colon cancer represents a clear example of these contradictory results, as it was reported to enhance cancer progression by enriching $LGR5^{+}$ stem cells; but at the same time supress cancer progression through inhibiting Wnt/β-Catenin signalling leading to a reduction in cancer cell proliferation and metastases formation [4,6,10]. This current article by Zhang et al. provides an in depth view about the enhancing role of the R-Spondin 2-LGR4 system in TSCC progression [9]. The evidence provided in this article are quite strong, especially since it covers several aspects of tumour progression, includes patient tissue samples, and *in vitro* and *in vivo* experiments. It is important to note that the authors showed that a high Rspo2 expression associated significantly with lymph node metastasis. This is an especially important finding since one of the major problems for TSCC patients is the tendency for early metastasis of the disease to the regional lymph nodes followed by dissemination of the cancer and distant metastases formation. This observation could, together with the up-regulation of the epithelial-mesenchymal transition (EMT) properties by Rspo2, function as a driving force for the migratory and invasive behaviour of TSCC, as suggested by the authors.

Combining together all of the data provided in this article, it is clear that the Rspo2-LGR4 system participates in TSCC progression through five different ways. It enhances proliferation, migration, invasion, EMT and stem-like properties of cancer cells. The study also represents an important advance in understanding the molecular mechanism behind the role of the Rspo2-LGR4 system in TSCC progression, as the authors investigated the signalling pathways underlying this system. Supported by previous publications, the authors were able to prove that the Rspo2-LGR4 system works through the Wnt/β-catenin signalling pathway [7,8].

One of the main questions which remains unanswered and requires further profound study is the role of the Rspo2-LGR4 system in metastases formation of the SCC cells - this needs to be tested *in vivo*. In the newly accepted article by Zhang et al. a murine ectopic tumour xenograft model was used to demonstrate the effect of Rspo2-LGR4 system on tumour growth and cell proliferation [9]. Neither local invasion nor metastases formation were studied here, probably due to the limitations of this model which does not usually allow cancer cells to spread or enable metastatic growth. It will be interesting to analyse metastasis *in vivo* by using, for example, a murine orthotopic xenograft model where TSCC cells are injected into the tongue and carcinoma cells in neck lymph nodes are analysed. Additionally, a novel zebrafish larvae model could be used where TSCC cells are injected into the perivitelline space and metastatic cells are also detected in the tail.

From a clinical point of view, the current work reveals a novel molecule and a possible target for therapeutic purposes. Although the translational process from *in vitro* testing to clinical use is very long and has a high rate of failure - only 5% of compounds showing efficacy in *in vitro* tests were licensed following clinical trials [5] - the current study provides a stable base aiming to provide a new targeted therapy for TSCC patients.

DOI of original article: https://doi.org/10.1016/j.ebiom.2019.03.076.
* Corresponding author at: Department of Oral and Maxillofacial Diseases, Clinicum, Biomedicum Helsinki 1, C223b P.O. Box 63 (Haartmaninkatu 8), University of Helsinki, 00014 Helsinki, Finland.
E-mail address: ahmed.al-samadi@helsinki.fi (A. Al-Samadi).

https://doi.org/10.1016/j.ebiom.2019.05.033

Author disclosure

The authors declare no conflicts of interest.

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.

[2] Coussy F, Lallemand F, Vacher S, Schnitzler A, Chemlali W, Caly M, et al. Clinical value of R-spondins in triple-negative and metaplastic breast cancers. Br J Cancer 2017; 116(12):1595–603.

[3] De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE—5-a population-based study. Lancet Oncol 2014;15(1):23–34.

[4] Dong X, Liao W, Zhang L, Tu X, Hu J, Chen T, et al. RSPO2 suppresses colorectal cancer metastasis by counteracting the Wnt5a/Fzd7-driven noncanonical Wnt pathway. Cancer Lett 2017;402:153–65.

[5] Hutchinson L, Kirk R. High drug attrition rates—where are we going wrong? Nat Rev Clin Oncol 2011;8(4):189–90.

[6] Wu C, Qiu S, Lu L, Zou J, Li WF, Wang O, et al. RSPO2-LGR5 signaling has tumour-suppressive activity in colorectal cancer. Nat Commun 2014;5:3149.

[7] Yin X, Yi H, Wang L, Wu W, Wu X, Yu L. R-spondin 2 promotes proliferation and migration via the Wnt/β-catenin pathway in human hepatocellular carcinoma. Oncol Lett 2017;14(2):1757–65.

[8] Zhang H, Han X, Wei B, Fang J, Hou X, Lan T, et al. RSPO2 enhances cell invasion and migration via the WNT/β-catenin pathway in human gastric cancer. J Cell Biochem 2019;120(4):5813–24.

[9] Zhang L, Song Y, Ling Z, Li Y, Ren X, Yang J, et al. R-spondin 2-LGR4 system regulates growth, migration and invasion, epithelial-mesenchymal transition and stem-like properties of tongue squamous cell carcinoma via Wnt/β-catenin signaling. EBioMedicine 2019. https://doi.org/10.1016/j.ebiom.2019.03.076 (in press) https://www.ebiomedicine.com/article/S2352-3964(19)30221-X/fulltext.

[10] Zhang S, Han X, Wei B, Fang J, Wei H. RSPO2 enriches LGR5(+) spheroid colon cancer stem cells and promotes its metastasis by epithelial-mesenchymal transition. Am J Transl Res 2016;8(2):354–64.